Figures and figure supplements

Corticostriatal dynamics encode the refinement of specific behavioral variability during skill learning

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Mice learn a fast lever-pressing task, shaping their behavior to gradually approach the minimum frequency target. (A) Schematic of the training protocol, starting with magazine habituation and CRF training in the first 2 days, followed by 3 days of the fast press schedules (S1–S9) where we introduce an increasingly higher covert target, defined as the inverse of the sum of three consecutive inter-press intervals (IPIs). (B) Joint distribution of the frequency (log scale) for all individual IPIs, in the first, middle and last session of the fast press schedules, for all the

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Figure 1. Continued

20 animals. Vertical dashed lines correspond to the IPI threshold used for sequence definition (IPI = 2 s, 0.5 Hz) and the final covert target (IPI = 3/660 ms, 4.5 Hz). (C) Percentage of lever presses comprised within sequences. (D) Number of sequences performed per minute. (E) Left: Example of sequences performed by a representative animal, aligned at the time of sequence initiation. Individual lever presses are marked as black ticks, the full sequence duration is shaded in grey and the IPIs that meet the session minimum target are shaded in orange; Top right: Probability of a magazine check immediately after a successful covert target; Bottom right: Probability of a magazine check having occurred after a reinforced lever-press vs a non-reinforced lever-press. (F) Distance of all three consecutive IPIs (summed) from the final covert target (∑3 IPIs <660 ms, ~4.5 Hz). (G) Spread of the distance between all three consecutive IPIs (summed) around the final minimum frequency target. (H) Percentage of sequences containing the minimum frequency target of the last session (end-target: 3 IPIs <660 ms, ~4.5 Hz). Shaded areas correspond to mean ± SEM.

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Figure 1—figure supplement 1. Lever-pressing rate increased and shifted towards higher speeds with training, and performance increased or plateaued when task difficulty did not change in consecutive sessions. (A) Lever presses per minute ($F_{8,152} = 41.34, p < 0.0001$). (B) Percentage of reinforced sequences ($F_{8,152} = 57.31, p < 0.0001$, Post hoc comparisons: Fisher's LSD test, (0.75 Hz) Session 3 vs Session 4 $t_{152} = 3.847, p = 0.0002$; (3 Hz) Session 6 vs Session 7 $t_{152} = 0.7681, p = 0.4436$; (4.5 Hz) Session 8 vs Session 9 $t_{152} = 2.639, p = 0.0092$). Shaded areas correspond to mean ± SEM. (C, D) Histograms with distribution of instantaneous lever-press frequencies, using linear (C) and log scales (D), defined as the inverse of all the individual IPIs from the 20 animals. Vertical dashed lines correspond to the IPI threshold used for sequence definition (IPI = 2 s, 0.5 Hz) and the final minimum frequency target (IPI = 220 ms, 4.5 Hz).

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Figure 2. Variability of behavioral dimensions evolves independently as animals learn a motor task. (A, B) Frequency and duration of lever-press sequences (C–F) Variability, measured as the variance and Fano factor, for sequence frequency and sequence duration. (G–H) Fano factor of both frequency and duration, normalized to the first session, for the frequency and control tasks. Shaded areas correspond to mean ± SEM.
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**Figure 2**—**figure supplement 1**. Significant correlation between variability of number of presses and duration, but not between variability of frequency and duration. Scatter plots of the paired values, variances and Fano factors, for frequency/duration and number of presses/duration. Each point corresponds to one session of one individual animal, with darker colors depicting later sessions. Line corresponds to the best linear fit of all the data, with the correspondent $R^2$ value.

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Figure 3. Behavior variability is differentially modulated during training. (A, B) Comparison of frequency and duration between reinforced (RF) and non-reinforced (Non-RF) sequences. (C, D) Variance and (E, F) variability, measured as the Fano factor, for reinforced and non-reinforced sequences. Black lines correspond to mean values for non-reinforced sequences. Red lines correspond to mean values for reinforced sequences. Shaded areas correspond to mean ± SEM. DOI: 10.7554/eLife.09423.008
Figure 4. Trial-to-trial variability in corticostriatal circuits decreases throughout training. (A–D) Neuronal variability (measured as the Fano factor of firing rates) during sequence performance and baseline periods, for all the recorded neuronal units and exclusively for 'stable units', for both M1 (blue traces) and dorsal striatum (DS, red traces). (E–H) Firing rates during sequence performance and baseline, for all the recorded units and exclusively for stable units, for M1 (blue traces) and DS (red traces). (I, J) Fano factor (FF) and firing rate (FR) modulation relative to baseline values, for individual units recorded.

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across the training sessions (stable units) within DS (top colorplots) and M1 (bottom colorplots). Right panels depict average modulation. Shaded areas correspond to mean ± SEM.

**Figure 4—figure supplement 1.** Histological confirmation of electrode tip position and stable units criteria. (A) Depiction of electrode array tip localization for motor cortex (top) and DS (bottom) for each individual animal. (B) Example coronal brain slice magnification using cresyl violet staining for confirmation of electrodes position. Atlas adapted from Paxinos and Franklin (2004). (C) Illustration of an example stable cell. Diagram illustrating the criteria for stability of cells across different recording sessions (top left, c1: cluster centroid during one session, c2: centroid of the same cluster in the subsequent session, see 'Materials and methods'). Average waveform in each session (bottom left). Cluster projection using principal component analysis (PCA) across the training sessions (right).

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Figure 4—figure supplement 2. Neuronal variability around the first and last press of a sequence does not change with training. Fano factor calculated for 1 s intervals around the first (DS $F_{8,48} = 1.213$, $p = 0.3121$; M1 $F_{8,48} = 0.1374$, $p = 0.9971$) and last presses (DS $F_{8,48} = 0.5227$, $p = 0.8335$; M1 $F_{8,48} = 0.8677$, $p = 0.5499$) of a sequence. Red lines correspond to mean value for DS, blue lines correspond to mean value for M1. Shaded areas represent mean ± SEM.
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Figure 5. Neuronal variability dynamics are still evident when analysis is restricted to sequences with duration and frequency. (A, B) Frequency and duration of matched sequences. (C, D) Neuronal variability, measured as the Fano factor of the firing rate, for sequences of matched duration and frequency, for both recorded areas, during sequences and baseline. (E, F) Firing rates, for sequences of matched duration and frequency, during sequences and baseline. (G, H) Fano factor (FF) and firing rate (FR) modulation relative to baseline values, for individual units recorded across the training.
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sessions (stable units) within DS (top colorplots) and M1 (bottom colorplots), for sequences of matched duration and frequency. Right panels depict average modulation. Error bars correspond to mean ± SEM.

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Figure 6. Correlations between corticostriatal and behavioral variability emerge for specific behavioral features. (A) Example traces from a single animal representing variability, calculated as the Fano factor, using a moving window of five consecutive trials shifted by one for sequence frequency (dark blue trace), sequence duration (green trace), M1 units firing rate during sequences (blue trace) and baseline (grey trace), and DS units firing rate during sequences (red trace) and baseline (grey trace). Vertical dashed lines represent separation of different training sessions. Shaded areas correspond to mean ± SEM. (B) Correlation between the variability (FF) in M1 and DS. (C, D) Correlation between variability traces from neuronal firing rates in M1 (blue bars) or DS (red bars), and variability of sequence frequency or duration. Error bars denote correlation coefficient ± standard error of the correlation. *p < 0.05.

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Figure 6—figure supplement 1. No significant correlation was found between average firing rate and any of the behavior features. Correlation between the firing rate and (A) sequence frequency or (B) sequence duration. Error bars denote correlation coefficient ± standard error of the correlation. DOI: 10.7554/eLife.09423.014
Figure 6—figure supplement 2. Changing the number of trials used for Fano factor calculation did not affect the observed corticostriatal and neuronal/behavioral variability correlations. (A, B) Correlation between variability traces from neuronal firing rates of cortical and striatal units, and between neuronal variability and variability of sequence frequency and duration using 3 (A) or 7 (B) consecutive trials. Error bars denote correlation coefficient ± standard error of the correlation. *p < 0.05.
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Figure 7. Corticostriatal plasticity is necessary for the specific refinement of behavioral variability. (A) Schematic of the adapted training sessions for mutant animals and littermate controls. Animals would remain in the same training session until reaching a stable performance. (B) Distance of the sum of all three consecutive IPIs from the final covert target \((\sum(3\text{ IPIs}) < 660\text{ ms, } \sim 4.5\text{ Hz})\) in SPN NR1 mutants and littermate controls (C) Spread of the distance between three consecutive IPIs around the final covert target. (D–G) Behavior parameters and variability, measured as the Fano factor, during early and late training period.
late training sessions in SPN NR1 mutants and littermate controls groups. Bars correspond to mean, with data from individual animals plotted on the background (red: SPN NR1-KO; black: littermate controls).

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Figure 7—figure supplement 1. Bootstrapping statistics in the SPN NR1-KO data support the observations from the post hoc planned comparisons. Histograms depicting the sampled statistic (difference between the means of two groups), after sampling with replacement the original data 100,000 times. Red vertical lines correspond to the 5% confidence intervals. Green vertical line corresponds to the mean of the sampled data. Blue vertical line corresponds to the difference between the original data groups (H0). DOI: 10.7554/eLife.09423.018